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February 13, 2012

IRIS Submission Desk
US Environmental Protection Agency
Docket Center
1301 Constitution Avenue, N.W.
EPA West Room 3334
Mail Code 2822T
Washington, DC 20004

Dear IRIS Submission Desk:

Attached you will find an article set to appear in *Regulatory Toxicology and Pharmacology* authored by Dr. Lorenz Rhomberg of Exponent titled "Hypothesis-Based Weight-of-Evidence Evaluation of Methanol as a Human Carcinogen," which we are forwarding to you for submission to the docket for the Toxicological Review of Methanol (Cancer) under the Integrated Risk Information System. As acknowledged, this peer reviewed article was prepared with financial support from the Methanol Institute. The abstract for this paper notes:

"Recent scientific debate has focused on the potential for exposure to methanol to cause lymphomas in humans. The concern stems from a few animal studies reporting an association, although evidence suggests the studies may have been confounded by chronic respiratory infection. Although the toxicological evidence for methanol carcinogenesis is weak, two modes of action have been put forth, one involving metabolism of methanol to formaldehyde, followed by formaldehyde induction of lymphoma, and another involving oxidative stress caused by hydrogen peroxide release during catalase-induced metabolism of methanol to formaldehyde. In this article, we apply our Hypothesis-Based Weight-of-Evidence (HBWoE) approach to evaluate the evidence regarding methanol exposure and lymphoma, attending to how human, animal, and mode-of-action results inform one another, tracing the logic of inference within and across all studies, and articulating how one could account for the suite of available observations. ***Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations as we see them, we conclude that the apparent association between methanol exposure and lymphoma in some animal studies is weak and strains biological plausibility, and is better interpreted as due to confounding or to a mechanism not relevant in humans."***

With the cancer portion of the methanol assessment currently on hold, we believe that this paper provides critical guidance for approaching a weight-of-evidence review of methanol's carcinogenicity. Further, at the recent National Academy of Sciences BEST meeting, NCEA Acting Director Becki Clark noted that the IRIS program is "moving toward a standardized weight of evidence characterization for all health assessments." Given this statement, and the announcement by IRIS Acting Director Vincent Cogliano that the Agency would host a workshop later this year to explore various weight-of-evidence approaches, we would encourage you to give very careful consideration to the analysis conducted by Dr. Rhomberg and his team as you reexamine the draft methanol cancer assessment.

In the interest of transparency, we request that you post this letter and the accompanying article on the NCEA webpage devoted to the methanol assessment. To that purpose, the Methanol Institute has arranged for a license agreement from the publisher listing www.epa.gov as the posting web site (also attached).

Thank you for this additional opportunity to provide critical data to inform the IRIS Toxicological Review of Methanol (Cancer).

Sincerely,

Gregory Dolan
Acting CEO

CC: Paul Anastas
Kevin Teichman
Becki Clark
Vincent Cogliano
John Vandenberg
Jeff Gift